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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/44 — A1

(11) International Publication Number: **WO 98/22108**

(43) International Publication Date: 28 May 1998 (28.05.98)

(21) International Application Number: PCT/US97/20955

(22) International Filing Date: 17 November 1997 (17.11.97)

(30) Priority Data:

60/031,468	20 November 1996 (20.11.96)	US
9700559.9	13 January 1997 (13.01.97)	GB

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: TRIARYL SUBSTITUTED IMIDAZOLES AND METHODS OF USE

(57) Abstract

2–4–Diaryl–5–pyridylimidazoles are glucagon antagonists. The compounds block the action of glucagon at its receptor. Thus, the compounds can be used in the prophylaxis or treatment of disease states in mammals mediated by elevated levels of glucagon. Examples of such disease states include diabetes, obesity, hypertension, and cachexia and the like.

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TRIARYL SUBSTITUTED IMIDAZOLES AND METHODS OF USE

BACKGROUND OF THE INVENTION

The present invention relates to triaryl substituted imidazoles which antagonize the metabolic effect of glucagon.

Diabetes is a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose. Uncontrolled hyperglycemia is associated with an increased risk for microvascular and macrovascular diseases, including nephropathy, retinopathy, hypertension, stroke and heart disease. Control of glucose homeostasis is, therefore, a major approach to the treatment of diabetes.

Glucagon is a major counter regulatory hormone that attenuates the inhibition of liver gluconeogenesis by insulin. Glucagon receptors are found primarily in the liver, although their presence has been documented in kidney, pancreas, adipose tissues, heart, smooth muscles of vascular tissues, and some regions of the brain, stomach and adrenal glands.

Type II diabetics have elevated levels of plasma glucagon and increased rates of hepatic glucose production. The rate of hepatic glucose production positively correlates with fasting blood glucose levels in type II diabetics. Therefore, antagonists of glucagon are useful in improving insulin responsiveness in the liver, decreasing the rate of gluconeogenesis and lowering the rate of hepatic glucose output resulting in a decrease in the levels of plasma glucose.

A monoclonal antibody to glucagon (Glu-mAb) has been utilized to test the acute effects of attenuation of glucagon action in streptozotocin-treated diabetic rats (Brand et al., Diabetologia 37:985, 1994). In contrast to a control antibody, injection of Glu-mAb attenuated the postprandial increase in blood glucose in moderately hyperglycemic rats (ie., rats with a moderate impairment in insulin secretion). In severely hyperglycemic rats (ie., rats with severely impaired insulin secretion), Glu-mAb injection did not lower blood glucose levels, but potentiated the hypoglycemic effect of a suboptimal dose of insulin.

These data suggest that attenuation of the action of glucagon in these models leads to increased sensitivity to the action of insulin, but does not lead to decreased blood glucose levels in the absence of insulin. On the other hand, a monoclonal antibody to glucagon was effective in lowering plasma glucose levels in diabetic rabbits independent of insulin effects(Brand et al., Diabetes, 45:1076 (1996). While these data support the notion that antagonism of glucagon action will provide beneficial therapy for both type I and type II diabetics, this hypothesis could be more rigorously tested if a specific non-peptidyl glucagon antagonist were available.

The regulation of glucagon homeostasis is also mediated by the hormone insulin, produced in the β cells of the pancreas. Deterioration of these cells is typically observed in Type I diabetics, and abnormalities in the function of these cells may occur in patients presenting the symptoms of Type II diabetes. Thus, a glucagon antagonist might have utility in treating Type I diabetics.

The glucagon receptor is expressed in kidney tissues where glucagon has been demonstrated to have an effect on electrolyte homeostasis including the ions sodium, potassium, chloride, magnesium, calcium, and phosphate and the non-electrolytes urea and water (Ahloulay et al., *Am. J. Physiol.*, 269: F225, 1995). A glucagon antagonist may have use in treating disorders involving electrolyte imbalance. The kidney is also gluconeogenic in response to glucagon (Amores et al., *Molec. Cell. Biochem.*, 137: 117, 1994) and an antagonist would act to lower glucose production in kidney furthering the treatment of diabetes.

Glucagon receptors are present in the heart and in smooth muscles. Glucagon has a direct effect on cardiac output and heart rate (Glick et al., *Circ. Res.*, 22: 789 (1968); Farah, Pharm. Rev., 35: 181, 1983). A strong correlation has been observed in patients with hypertension and elevated plasma glucagon levels resulting from impaired hepatic catabolism (Silva et al., *Heptatology*, 11: 668, 1990). Antagonism of the effects of elevelated glucagon levels may have an effect on certain types of hypertension, thus a glucagon antagonist may

have utility in the treatment of certain types of hypertension associated with elevated glucagon production.

The primary role for glucagon and glucagon receptors associated with adipose tissues is to induce lipolysis, thus providing free fatty acids as a substrate for fat burning tissues (Saggerson et al., *Biochem. J.*, 238: 387, 1986). An antagonist to this effect might be useful in treating conditions where there is excessive lipolysis of fat stores resulting from elevated glucagon levels, such as wasting disease (cachexia).

Glucagon and glucagon receptors have been localized to the hippocampus region of the brain (Hoosein and Gurd, *Proc. Natl. Acad. Sci. USA*, 81: 4368, 1984). This discovery suggests that glucagon may have a neuroendocrine role in initiating or elaborating basic behavior or somatic motor programs. Since glucagon secretion is increased in response to low blood glucose levels, increased glucagon levels in the brain may initiate behavior to respond to low glucose levels, such as eating. Thus, chronic hyperglucagonemia may also result in a constant craving for food resulting in obesity. A glucagon antagonist may have utility in treating obesity by altering feeding behavior associated with a response to glucagon.

The compounds in the present invention are glucagon antagonists. The compounds block the action of glucagon at its receptors and thereby decrease the levels of plasma glucose. The instant compounds thus are useful as antidiabetic agents. Glucagon may have other direct effects on cardiac output, lipolysis, and feeding behavior and therefore may be useful as antihypertensive, anti-cachexia or antiobesity agents.

SUMMARY OF THE INVENTION

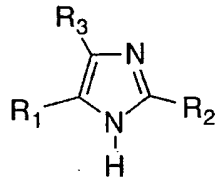
The present invention relates to 2,4-diaryl-5-pyridyl imidazoles which are glucagon receptor antagonists. These compounds are therefore useful for the treatment of diseases caused by excessive levels of glucagon, including diabetes and certain types of hypertension, cachexia and obesity.

Also included in the invention are pharmaceutical compositions which comprise a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included in the invention are methods of treating glucagon-mediated diseases, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective to treat said diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating glucagon-mediated diseases, in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a glucagon antagonist of formula (I):



(I)

wherein

R_1 is 4-pyridyl, 4-pyrimidinyl or 4-quinolyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) halogen,

(2) -CN,

(3) C_{1-10} alkyl-, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(4) -O-C_{1-10}alkyl,

(5) -S-C_{1-10}alkyl,

(6) -NR_8R_9, and

(7) -NO_2;

R_2 is phenyl, 1-naphthyl, 2-naphthyl or heteroaryl which is unsubstituted or substituted with one, two or three substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl,

(2) R_4, and

(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4;

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to fivesubstituents each of which is independently selected from the group consisting of

(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(2) -O-C_{1-2}alkyl,

(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,

(4) -O-heteroaryl,

(5) $-NO_2$,

(6) halogen,

(7) $-S-CH_3$,

(8) $-S(O)_mC_{1-2}$alkyl,

(9) $-S(O)_mOR_8$,

(10) $-S(O)_mNR_8R_9$,

(11) $-O(CR_{10}R_{20})_pNR_8R_9$,

(12) $-C(O)C_{1-2}$alkyl,

(13) $-CO_2C_{1-2}$alkyl,

(14) $-CO_2(CR_{10}R_{20})_nCONR_8R_9$,

(15) $-ZC(O)R_8$,

(16) -CN,

(17) $-C(Z)NR_8R_9$,

(18) amino,

(19) $NR_{10}C(Z)R_8$,

(20) $-C(Z)NR_8OR_9$,

(21) $NR_{10}C(Z)NR_8R_9$,
(22) $-NR_{10}S(O)_mR_{11}$,
(23) $-C(=NOR_{21})R_8$,
(24) $-NR_{10}C(=NR_{15})SR_{11}$,
(25) $-NR_{10}C(=NR_{15})NR_8R_9$,
(26) $-NR_{10}C(=CR_{14}R_{24})SR_{11}$,
(27) $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$,
(28) $-NR_{10}C(O)C(O)NR_8R_9$,
(29) $-NR_{10}C(O)C(O)OR_{10}$,
(30) $-NR_{10}S(O)mNR_7R_{17}$,
(31) $-C(=NR_{13})NR_8R_9$,
(32) $-C(=NOR_{13})NR_8R_9$,
(33) $-C(=NR_{13})ZR_{11}$,
(34) $-OC(Z)NR_8R_9$,
(35) $-NR_{10}S(O)_mCF_3$,
(36) $-NR_{10}C(Z)OR_{10}$,
(37) 5-(R_{18})-1,2,4-oxadiazol-3-yl or
(38) 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

R_4 is

(1) $-OR_8$,
(2) $-NO_2$,
(3) halogen
(4) $-S(O)_mR_{11}$,
(5) $-SR_8$,
(6) $-S(O)_mOR_8$,
(7) $-S(O)_mNR_8R_9$,
(8) $-NR_8R_9$,
(9) $-O(CR_{10}R_{20})_pNR_8R_9$,
(10) $-C(O)R_8$,
(11) $-CO_2R_8$,
(12) $-CO_2(CR_{10}R_{20})_nCONR_8R_9$,
(13) $-ZC(O)R_8$,
(14) -CN,
(15) $-C(Z)NR_8R_9$,

(16) $NR_{10}C(Z)R_8$,
(17) $-C(Z)NR_8OR_9$,
(18) $NR_{10}C(Z)NR_8R_9$,
(19) $-NR_{10}S(O)_mR_{11}$,
(20) $-C(=NOR_{21})R_8$,
(21) $-NR_{10}C(=NR_{15})SR_{11}$,
(22) $-NR_{10}C(=NR_{15})NR_8R_9$,
(23) $-NR_{10}C(=CR_{14}R_{24})SR_{11}$,
(24) $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$,
(25) $-NR_{10}C(O)C(O)NR_8R_9$,
(26) $-NR_{10}C(O)C(O)OR_{10}$,
(27) $-C(=NR_{13})NR_8R_9$,
(28) $-C(=NOR_{13})NR_8R_9$,
(29) $-C(=NR_{13})ZR_{11}$,
(30) $-OC(Z)NR_8R_9$,
(31) $-NR_{10}S(O)_mCF_3$,
(32) $-NR_{10}C(Z)OR_{10}$,
(33) 5-(R_{18})-1,2,4-oxadiazol-3-yl,
(34) 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl or
(35) azido;

R_7 and R_{17} are each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 and R_9 are independently selected from

(1) hydrogen,
(2) heterocyclyl,
(3) heterocyclylalkyl, and
(4) R_{11}; or

R_8 and R_9 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is (1) C_{1-10} alkyl,
(2) halo-substituted C_{1-10} alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10} alkynyl,
(5) C_{3-7} cycloalkyl,
(6) C_{5-7} cycloalkenyl,
(7) aryl,
(8) aryl-C_{1-10} alkyl,
(9) heteroaryl or
(10) heteroaryl-C_{1-10} alkyl;

R_{12} is (1) hydrogen,
(2) $-C(Z)R_{13}$,
(3) optionally substituted C_{1-4} alkyl,
(4) optionally substituted aryl C_{1-4} alkyl, or
(5) $S(O)_2R_{25}$;

R_{13} is (1) hydrogen, or
(2) R_{25};

R_{14} and R_{24} is each independently selected from
(1) hydrogen,
(2) alkyl,
(3) nitro or
(4) cyano;

R_{15} is (1) hydrogen,
(2) cyano,
(3) C_{1-4} alkyl,
(4) C_{3-7} cycloalkyl or
(5) aryl;

R_{18} and R_{19} is each independently selected from
(1) hydrogen,
(2) C_{1-4} alkyl,
(3) substituted alkyl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy,

(4) optionally substituted aryl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy,

(5) optionally substituted arylalkyl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy, or

R_{18} and R_{19} together denote an oxo or thioxo;

R_{21} is (1) R_{13},

(2) a pharmaceutically acceptable cation, or

(3) aroyl, or

(4) C_{1-10} alkanoyl;

R_{22} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{25} is (1) C_{1-10} alkyl,

(2) C_{3-7} cycloalkyl,

(3) heterocyclyl,

(4) aryl,

(5) aryl C_{1-10} alkyl,

(6) heterocyclyl-C_{1-10} alkyl,

(7) heteroaryl or

(8) heteroaryl C_{1-10} alkyl;

Z is oxygen or sulfur;

m is 1 or 2;

n is 1 to 10;

p is 1 to 10; or

a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the compounds of formula I are those wherein

R_1 is 4-pyridyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) halogen,

(2) -CN,

(3) C_{1-10} alkyl-, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(4) -O-C_{1-10}alkyl,

(5) -S-C_{1-10}alkyl,

(6) -NR_8R_9, and

(7) -NO_2.

In another preferred embodiment the compounds of formula I are those wherein

R_2 is phenyl, 1-naphthyl, 2-naphthyl or thienyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl,

(2) R_4, and

(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4.

In yet another embodiment the compounds of formula I are those wherein

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to five substituents each of which is independently selected from the group consisting of

(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(2) -O-C_{1-2}alkyl,

(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,

(4) -O-heteroaryl,

(5) -NO_2,

(6) halogen,

(7) -S-CH_3,

(8) -$S(O)_m$$C_{1-2}$alkyl,

(9) -$S(O)_m$$OR_8$.

In a more preferred embodiment the compounds of formula I are those wherein

R_1 is 4-pyridyl unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,
(2) -O-C_{1-10}alkyl,
(3) -S-C_{1-10}alkyl,
(4) $-NR_8R_9$, and
(5) $-NO_2$;

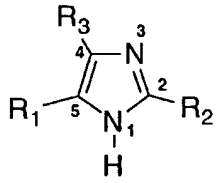
R_2 is phenyl, 1-naphthyl, 2-naphthyl or thienyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of
(1) C_{1-10} alkyl,
(2) R_4, and
(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4;

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to five substituents each of which is independently selected from the group consisting of
(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,
(2) -O-C_{1-2}alkyl,
(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,
(4) -O-heteroaryl,
(5) $-NO_2$,
(6) halogen,
(7) $-S-CH_3$,
(8) $-S(O)_mC_{1-2}$alkyl,
(9) $-S(O)_mOR_8$,

R_4 is
(1) $-OR_8$,
(2) $-NO_2$,
(3) halogen
(4) $-S(O)_mR_{11}$,

(5) $-SR_8$,
(6) $-S(O)_mOR_8$,
(7) $-S(O)_mNR_8R_9$,
(8) $-NR_8R_9$,
(9) $-O(CR_{10}R_{20})_pNR_8R_9$,
(10) $-C(O)R_8$,
(11) $-CO_2R_8$,
(12) $-CO_2(CR_{10}R_{20})_nCONR_8R_9$,
(13) $-ZC(O)R_8$,
(14) -CN,
(15) $-C(Z)NR_8R_9$,
(16) $NR_{10}C(Z)R_8$,
(17) $-C(Z)NR_8OR_9$,
(18) $NR_{10}C(Z)NR_8R_9$,
(19) $-NR_{10}S(O)_mR_{11}$,
(20) azido.

For the purposes herein of nomenclature, the compounds of formula I are named by their position corresponding to:



In another aspect of the present invention, there are provided compounds listed below. These compounds are also especially preferred for the treatment of diabetes:

(1) 4-(4-fluorophenyl)-2-(4-methoxycarbonylphenyl)-5-(4-pyridyl)imidazole,
(2) 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(3) 2-(4-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(4) 4-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-(4-pyridyl)imidazole,
(5) 2-(4-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(6) 4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)imidazole,
(7) 4-(4-fluorophenyl)-2-(4-n-heptyphenyl)-5-(4-pyridyl)imidazole,
(8) 4-(4-fluorophenyl)-2-(4-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(9) 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole,
(10) 2-(4-aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(11) 2-(3-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(12) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(13) 2-(3,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(14) 4-(4-fluorophenyl)-2-(4-iodophenyl)-5-(4-pyridyl)imidazole,
(15) 2-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(16) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(4-trifluoromethylphenyl)imidazole,
(17) 2-(4-biphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(18) 4-(4-fluorophenyl)-2-(1-naphthyl)-5-(4-pyridyl)imidazole,
(19) 2-(4-ethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(20) 4-(4-fluorophenyl)-2-(2-naphthyl)-5-(4-pyridyl)imidazole,
(21) 2-(5-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(22) 4-(4-fluorophenyl)-2-(3-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(23) 2-(4-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(24) 4-(4-fluorophenyl)-2-(4-methylphenyl)-5-(4-pyridyl)imidazole,
(25) 2-(3-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(26) 2-(3-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(27) 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(28) 2-(3-bromo-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(29) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(30) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(3-trifluoromethylphenyl)imidazole,
(31) 2-(3,4-dimethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(32) 2-(3-chlorophenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,
(33) 4-(3-chlorophenyl)-2-(3,4-dichlorophenyl)-5-(4-pyridyl)imidazole,
(34) 2-(4-benzyloxyphenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,
(35) 2-(3,4-dichlorophenyl)-4-phenyl-5-(4-pyridyl)imidazole,
(36) 2-(4-benzyloxyphenyl)-4-phenyl-5-(4-pyridyl)imidazole,
(37) 2-(4-bromophenyl)-4-phenyl-5-(4-pyridyl)imidazole,
(38) 2-(4-(2-chloro-6-fluorobenzyloxy)phenyl)-4-(4-fluorophenyl-5-(4-pyridyl)imidazole,
(39) 2-(4-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(40) 2-(3-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,
(41) 2-(3-chlorophenyl)-4-(4-iodophenyl)-5-(4-pyridyl)imidazole,
(42) 2-(4-chlorophenyl)-4-(4-bromophenyl)-5-(4-pyridyl)imidazole,
(43) 2-(4-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,
(44) 2-(3-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,
(45) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(3-methyl-4-pyridyl)imidazole,
(46) 2-(4-chlorophenyl)-4-(2-fluoro-4-trifluoromethylphenyl)-5-(4-pyridyl)imidazole,
(47) 2-(4-chlorophenyl)-4-(2-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(48) 4-(3-bromophenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,
(49) 4-(3-bromo-4-methoxyphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,
(50) 2-(4-chlorophenyl)-4-(2-ethoxyphenyl)-5-(4-pyridyl)imidazole, and
(51) 2-(4-Azidophenyl)-4-(3-iodophenyl)-5-(4-pyridyl)imidazole.

The invention is described herein in detail using the terms defined below unless otherwise specified.

"Halogen" includes fluorine, chlorine, bromine and iodine.

The term "alkyl" refers to a monovalent alkane (hydrocarbon)-derived radical containing the designated number of carbon atoms. It may be straight or branched. Examples include methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, sec-butyl, isopentyl and t-butyl.

The term "cycloalkyl" refers to a cyclized alkane (hydrocarbon)-derived radical containing the designated number of carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "alkenyl" refers to a hydrocarbon radical, straight or branched, containing the designated number of carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include ethenyl, propenyl, butenyl and isobutenyl.

The term "alkynyl" refers to a hydrocarbon radical, straight or branched, containing the designated number of carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Examples of alkynyl groups include ethynyl, propynyl and butynyl.

Aryl refers to aromatic rings including phenyl and naphthyl.

The term "heteroaryl" (on its own or in any combination, such as "heteroaryloxy") represents a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O and S, such as, but not limited to pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, tetrazolyl, triazolyl, oxadiazolyl, oxazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, 2,3-dihydrobenzofuranyl, quinolinyl, isoquinolinyl, benzotriazolyl, benzoxazolyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, purinyl, furopyridine and thienopyridine, tetrahydrobenzothiazolyl, 5,6,7,8-tetrahydroquinolinyl, 2,3-cyclopentenopyridyl, 4,5,6,7-tetrahydroindolyl, 5,6,7,8-tetrahydroisoquinolyl, and 5,6,7,8-tetrahydroquinoxalinyl.

"Heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") represents a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O and S. Examples of heterocyclyls are piperidinyl, morpholinyl,

pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazo[4,5-c]pyridine, imidazolinyl, piperazinyl, pyrazolindinyl and the like.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included within the scope of the present invention.

Throughout the instant application, the following abbreviations are used with the following meanings:

Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
CBZ, Cbz	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DCM	dichloromethane
DIEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
DSC	N,N'-disuccinimidyl carbonate
DTT	dithiothreitol
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
HBGF	hemogloblin growth factor
HOAc	acetic acid
HPLC	High pressure liquid chromatography
HOBT, HOBt	Hydroxybenztriazole
HS	human serum
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
PBS	phosphate buffer saline
Ph	phenyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

The pharmaceutically acceptable salts of the compounds of formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of formula I formed e.g. from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric,

toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

This invention relates to a method of inhibiting the action of glucagon at its receptors thereby reducing the rate of gluconeogenesis and the concentration of glucose in plasma. Thus, compounds of formula I can be used in the prophylaxis or treatment of disease states in mammals mediated by elevated levels of glucagon. Examples of such disease states include diabetes, obesity, hypertension, and cachexia and the like.

The compounds of formula I are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. This invention, therefore, also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The pharmaceutical carrier employed may be, for example, solid or liquid. Solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Liquid carriers include syrup, peanut oil, olive oil, water and the like. Similarly, the carrier may include time delay material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

The compounds of formula I are administered in conventional dosage forms prepared by combining a compound of formula I with standard pharmaceutical carriers according to conventional procedures. The compounds of formula I may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

These active compounds may also be administered parenterally, for example intravenously, intramuscularly, intradermally or subcutaneously. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary

conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds of formula I may also be administered topically in the form of a liquid, solid or semi-solid. Liquids include solutions, suspensions and emulsions. Solids include powders, poultices and the like. Semi-solids include creams, ointments, gels and the like.

Drops according to the present invention may comprise sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous liquid, with the aid of suitable machinery, with a

greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

Compounds of the present invention may also be administered intranasally as, for example, liquid drops or spray; by intranasal or oral inhalation; rectally; trasdermally; or vaginally.

The amount of a compound of formula I, for the methods of use disclosed herein, vary with the compound chosen, the mode of administration, the nature and severity of the condition being treated, and other factors left to the discretion of the physician. A representative dosing regimen for treating diabetes mellitus and/or hyperglycemia may involve administering a compound of formula I at a daily dosage of from about 0.001 milligram to about 100 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

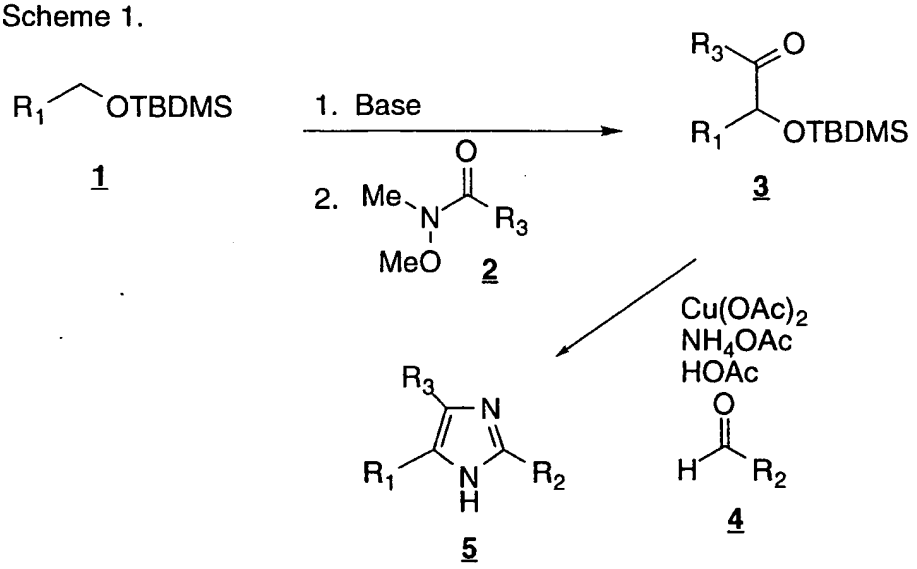
Compounds similar to Formula I have been described previously as cytokine inhibitors (WO93/14081; WO95/03297), antiinflammatory agents (WO96/03387), and protein kinase inhibitors (WO96/18626). None of these publications describe or claim treatment of diabetes by antagonism of the glucagon receptor.

Compounds of the present invention may be prepared by several general synthetic methods as described in, for example, M. R. Grimmett, *Comprehensive Heterocyclic Chemistry, The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds,* A. R.

Katritzky and C. W. Rees, eds., Vol. 5, Pergamon Press, Oxford, 1984, pp. 457-498. The compounds of the present invention can be prepared by procedures illustrated in the accompanying schemes. The three general methods for preparation of the imidazole nucleus are outlined in Schemes 1 and 2.

In the first method (Scheme 1), a suitably protected alcohol (1) (e.g., when R_1 is 4-pyridyl, (1) is 4-(t-butyldimethylsilyloxymethylpyridine), is deprotonated with a strong base such as lithium diisopropyl amide or n-butyl lithium and the resulting anion is reacted with an appropriate N,O-dimethylhydroxamide (2) to give a protected α-hydroxy ketone (3). The protected α-hydroxy ketone is then condensed with a suitably functionalized aldehyde (4) in the presence of copper(II) acetate and ammonium acetate in acetic acid to form the desired compound (5).

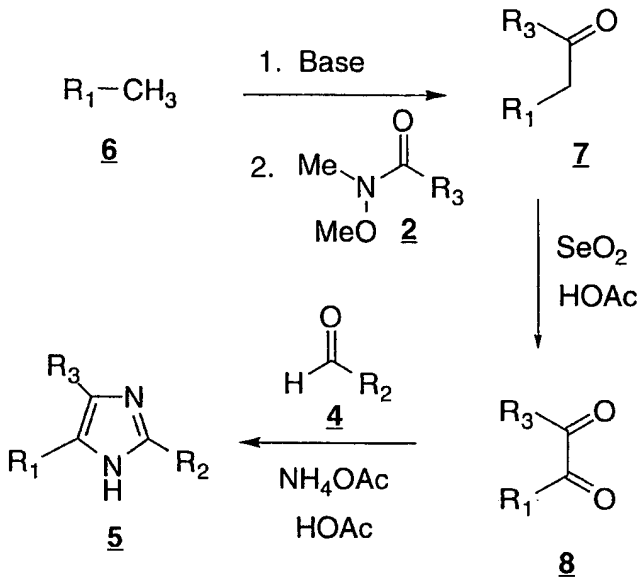
Scheme 1.



In the second method (Scheme 2), an heteroarylmethane (6) (e.g., when R_1 is 4-pyridyl, (6) is 4-picoline) is deprotonated with a strong base such as lithium diisopropyl amide or n-butyl lithium and the resulting anion is reacted with N,O-dimethylhydroxamide (2) to give a ketone (7). The dione (8) is obtained by selenium dioxide oxidation of

the ketone (7) and then condensed with a suitably functionalized aldehyde (4) in the presence of ammonium acetate in acetic acid to form the desired imidazole (5).

Scheme 2.

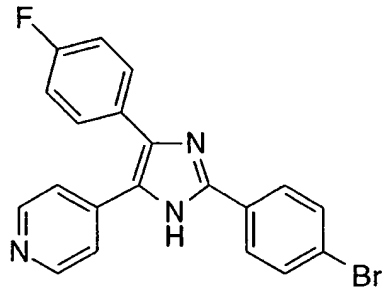


In the various synthetic methods described above, protection and deprotection of functional groups such as hydroxyl and amino groups may be required. The selection of the appropriate protecting groups, and methods for introducing and removing the protecting groups are within the knowledge of one skilled in the art, and are also described in standard reference books such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., John Wiley & Sons, Inc., 1991.

The following examples are provided to more fully illustrate the invention, and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLE 1

2-(4-Bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole



Step A: 4-t-Butydimethylsilyloxymethylpyridine

To a solution of 4-pyridylcarbinol (50.3 g, 0.46 mol) in methylene chloride (250 mL) under a dry nitrogen atmosphere was added triethylamine (97 mL, 0.69 mol). To this mixture was added dropwise tert-butyl-dimethylsilyl chloride (83.7 g, 0.555 mol) with cooling (T 34 °C). The reaction mixture was stirred overnight at room temperature.. The slurry was then filtered and the solvent removed by rotoevaporation. The residue was suspended in toluene and filtered and the solvent removed by rotoevaporation. The residue was suspended in diethyl ether and filtered and the solvent removed by rotoevaporation. The same process was repeated with hexanes to yield 4-t-butydimethylsilyloxymethylpyridine as a brown oil.

Step B: 4-Fluoro-N-methoxy-N-methyl-benzamide

To a stirred, cooled suspension of N,O-dimethylhydroxylamine hydrochloride (67.7 g, 0.69 mol) in methylene chloride (750 mL) at 0 °C was added dropwise triethylamine (211 mL, 1.51 mol). To this mixture was added dropwise 4-fluorobenzoyl chloride (100 g, 0.63 mol) over a 35 min period. After the addition was complete, the reaction mixture was stirred at room temperature overnight. A fine precipitate formed. The reaction mixture was filtered and the filtrate added to water (2 L). The organic phase was separated and washed successively with water and saturated salt solution. After drying the solution over anhydrous magnesium sulfate, the solvent was removed by rotoevaporation. The residue was azeotroped with toluene and the solvent removed by rotoevaporation and pumping under high vacuum to yield the title compound as a golden yellow oil.

Step C. 4-Pyridyl-t-butydimethylsilyloxymethyl 4-fluorophenyl ketone

Into a 2 L 3-necked round bottom flask fitted with a thermometer, dry nitrogen gas inlet, addition funnel and mechanical stirrer was added diisopropylamine (65 mL, 0.46 mol) in THF (120 mL). Cooled to -20 °C with a isopropyl alcohol/ dry ice bath and added a solution of n-butyllithium in hexanes (210 mL of a 2.5 M solution, 0.53 mol). Stirred at -15 °C for 30 min, then cooled to -20 °C. Added 4-t-butydimethylsilyloxymethylpyridine (98.2 g, 0.44 mol) neat over a 30 min period. Let stir for 45 min at -20 °C. To this mixture was added a solution of 4-fluoro-N-methoxy-N-methyl-benzamide (84.5 g, 0.46 mol) in THF (90 mL) over a 30 min period. The dark solution was stirred at 0 °C for 1 h, then warmed slowly to room temperature for 30 min. The reaction was poured into water (500 mL) containing ammonium chloride (100 g). After stirring for 10 min at room temperatue, the solution was extracted with ethyl acetate (3 times). The combined organic extracts were washed successively with water and saturated salt solution. The combined aqueous layers were extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 15-50% ethyl acetate in hexanes (17 L in total). The solvent was removed by rotoevaporation to yield the title compound as an amber oil (120.4 g, 74% yield).

Step D: 2-(4-Bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

To a solution of 4-pyridyl-t-butydimethylsilyloxymethyl 4-fluorophenyl ketone from Step C (100 mg, 0.29 mmol) in acetic acid (2 mL) was added copper(II) acetate (105.1 mg, 0.58 mmol) followed by solid ammonium acetate (222 mg, 2.89 mmol) and 4-bromobenzaldehyde (66.8 mg, 0.36 mmol). The reaction was stirred at 100 °C for 2.5 h and then cooled to 0 °C. Ice (1.5 g) and ethyl acetate (3 mL) were added. Ammonium hydroxide solution (4 mL) was added dropwise. Saturated ammonium chloride solution (1.5 mL) was added and the reaction mixture stirred at room temperature for 30 min. The phases were separated and the aqueous phase extracted with ethyl acetate (2 times). The combined organic phases were successively washed

with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 1-2% methanol in methylene chloride. The title compound was homogeneous by TLC and isolated as a yellow solid (67 mg, 59% yield, mp. 274-5 °C), mass spectrum (CI) m/e = 394, 396 $(M+1)^+$.

The following compounds were prepared by methods analogous to those described in Example 1 except the appropriately substituted N-methoxy-N-methylbenzamide and substituted benzaldehyde was used in place of 4-fluoro-N-methoxy-N-methylbenzamide and 4-bromobenzaldehyde, respectively.

4-(4-fluorophenyl)-2-(4-methoxycarbonylphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 374 $(M+1)^+$.

2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 341 $(M+1)^+$.

2-(4-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 422 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 358 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 361 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-n-heptyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 430 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-phenoxyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 408 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 346 $(M+1)^+$.

2-(3-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 394, 396 $(M+1)^+$.

2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 350 $(M+1)^+$.

2-(3,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 384, 386 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-iodophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 442 $(M+1)^+$.

2-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 384, 386 $(M+1)^+$.

4-(4-fluorophenyl)-5-(4-pyridyl)-2-(4-trifluoromethylphenyl)imidazole, mass spectrum (CI) m/e = 384 $(M+1)^+$.

2-(4-biphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 392 $(M+1)^+$.

4-(4-fluorophenyl)-2-(1-naphthyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366 $(M+1)^+$.

2-(4-ethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 344 $(M+1)^+$.

4-(4-fluorophenyl)-2-(2-naphthyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366 $(M+1)^+$.

2-(5-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 400, 402 $(M+1)^+$.

4-(4-fluorophenyl)-2-(3-phenoxyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 408 $(M+1)^+$.

2-(4-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 400, 402 $(M+1)^+$.

4-(4-fluorophenyl)-2-(4-methylphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 330 $(M+1)^+$.

2-(3-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 422 $(M+1)^+$.

2-(3-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 350 $(M+1)^+$.

2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 352 $(M+1)^+$.

2-(3-bromo-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 412, 414 $(M+1)^+$.

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 368 $(M+1)^+$.

4-(4-fluorophenyl)-5-(4-pyridyl)-2-(3-trifluoromethylphenyl)imidazole, mass spectrum (CI) m/e = 384 $(M+1)^+$.

2-(3,4-dimethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 344 $(M+1)^+$.

2-(3-chlorophenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366 $(M+1)^+$.

4-(3-chlorophenyl)-2-(3,4-dichlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 400, 402 $(M+1)^+$.

2-(4-benzyloxyphenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 400, 402 $(M+1)^+$.

2-(3,4-dichlorophenyl)-4-phenyl-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366, 368 $(M+1)^+$.

2-(4-benzyloxyphenyl)-4-phenyl-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 404 $(M+1)^+$.

2-(4-bromophenyl)-4-phenyl-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 376, 378 $(M+1)^+$.

2-(4-(2-chloro-6-fluorobenzyloxy)phenyl)-4-(4-fluorophenyl-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 474 $(M+1)^+$.

2-(4-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366 $(M+1)^+$.

2-(3-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 366 $(M+1)^+$.

2-(3-chlorophenyl)-4-(4-iodophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 458 $(M+1)^+$.

2-(4-chlorophenyl)-4-(4-bromophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 410, 412 $(M+1)^+$.

2-(4-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole, mass spectrum (CI) m/e = 400 $(M+1)^+$.

2-(3-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole, mass spectrum (CI) m/e = 400 $(M+1)^+$.

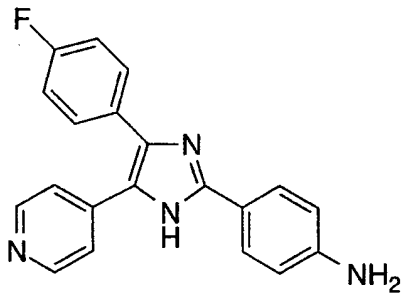
2-(4-chlorophenyl)-4-(2-phenoxyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 424 $(M+1)^+$.

4-(3-bromo-4-methoxyphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 440, 442 $(M+1)^+$.

2-(4-chlorophenyl)-4-(2-ethoxyphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 376 $(M+1)^+$.

EXAMPLE 2

2-(4-Aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

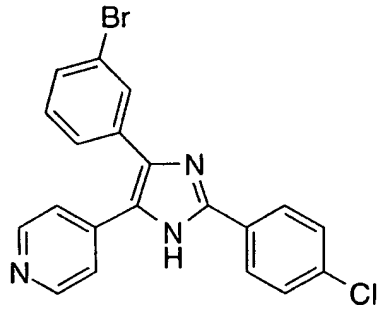


A solution of 2-(4-nitrophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole (prepared according to the method described in Example 1, 25 mg, 0.07 mmol) in ethanol (2 mL) and ethyl acetate (1 mL) containing 10% palladium on carbon (12 mg) was stirred under a hydrogen atmosphere (1 atm) for 4 h. The contents of the flask were centrifuged to remove the catalyst. The solvent was removed and the catalyst washed and centrifuged with fresh ethyl acetate (3 times). The combined organic phases were rotoevaporated and the residue purified by flash column chromatography on silica gel eluted with 0-

5% methanol in methylene chloride. The desired fractions were collected, combined and the solvent removed by rotoevaporation to yield the title compound as a yellow solid (20 mg, 88% yield), mass spectrum (CI) m/e = 331 $(M+1)^+$.

EXAMPLE 3

4-(3-Bromophenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole



Step A: 3-Bromo-N-methoxy-N-methylbenzamide.

To a mixture of N,O-dimethylhydroxylamine hydrochloride (4.8 g, 50 mmol) in methylene chloride (50 mL) was added dropwise triethylamine (11.1 g, 109 mmol). After cooling to 0 °C, a solution of 3-bromobenzoyl chloride (10 g, 45.6 mmol) in methylene chloride (10 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature. The contents of the reaction flask were filtered through a pad of celite filter aid wet with diethyl ether. The filter pad was subsequently washed twice with fresh diethyl ether. The solvent of the combined organic phases was removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 0-50% ethyl acetate in hexanes. The title compound was isolated as a thick, colorless gum (9.46 g, 85% yield).

Step B: 3-Bromophenyl 4-pyridylmethyl ketone

To a solution of LDA (prepare from diisopropylamine (2.17 g, 21.5 mmol) in THF (6 mL) and n-butyllithium (9.8 mL of a 2.5M solution in

hexanes) at -78 °C was added dropwise a solution of 4-picoline (1.82 g, 19.5 mmol) in THF (6 mL). The reaction mixture was stirred at -78 to -30 °C for 45 min. The reaction mixture was then cooled to -78 °C and a solution of 3-bromo-N-methoxy-N-methylbenzamide (5 g, 20.5 mmol) in THF (6 mL) was added dropwise. The reaction mixture was stirred for 1 h with gradual warming to -30 °C. The reaction was then quenched with saturated ammonium chloride solution (5 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (2 times). The combined organic phases were washed successively with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the crude product purified by flash column chromatography on silica gel eluted with 0-50% ethyl acetate in hexanes. The title compound was isolated as a cream-colored solid (785 mg, 14 % yield), mass spectrum (CI) m/e = 276, 278 $(M+1)^+$.

Step C: 1-(3-Bromophenyl)-2-(4-pyridyl)-ethane-1,2-dione

To a solution of 3-bromophenyl 4-pyridylmethyl ketone (prepared according to Step B, 1.978 g, 7.17 mmol) in acetic acid (50 mL) was added selenium dioxide powder (796 mg, 7.17 mmol). The reaction mixture was stirred at 100 °C for 40 min. The reaction was then cooled to 0 °C and saturated solution of potassium carbonate was added until the pH ~ 9. The mixture was extracted with ethyl acetate (2 times) and the combined organic phases washed successively with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the crude product purifed by flash column chromatography on silica gel eluted with 10-50% ethyl acetate in hexanes. The title compound was isolated as a pale yellow solid (807 mg, 39% yield).

Step D: 4-(3-Bromophenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole

To a solution of 1-(3-bromophenyl)-2-(4-pyridyl)-ethane-1,2-dione from Step C (400 mg, 1.38 mmol) in acetic acid (10 mL) was added ammonium acetate (1.06 g, 13.8 mmol) and 4-chlorobenzaldehyde (242 mg,

1.72 mmol). The reaction mixture was stirred at 100 °C for 3 h. The reaction was cooled to 0 °C and ice and ethyl acetate were added. Concentrated ammonium hydroxide solution was added to pH ~10. The layers were separated and the aqueous phase extracted with ethyl acetate (2 times). The organic phases were combined and washed successively with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the crude product purified by flash column chromatography on silica gel eluted with 0-3% methanol in methylene chloride. The title compound was isolated as a pale yellow-orange solid (270 mg, 48% yield), mass spectrum (CI) m/e = 410, 412 $(M+1)_+$.

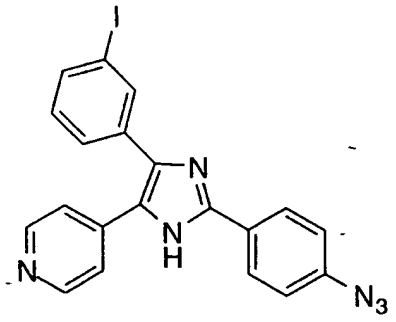
The following compounds were prepared by methods analogous to those described in Example 3 except the appropriately substituted N-methoxy-N-methylbenzamide and substituted 4-picoline was used in place of 4-fluoro-N-methoxy-N-methylbenzamide and 4-picoline, respectively.

2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(3-methyl-4-pyridyl)imidazole, mass spectrum (CI) m/e = 364 $(M+1)^+$.

2-(4-chlorophenyl)-4-(2-fluoro-4-trifluoromethylphenyl)-5-(4-pyridyl)imidazole, mass spectrum (CI) m/e = 418 $(M+1)^+$.

EXAMPLE 4

2-(4-Azidophenyl)-4-(3-iodophenyl)-5-(4-pyridyl)imidazole



Step A: N-Methoxy-N-methyl-3-iodobenzamide

EDC (6.91 g, 36 mmole) was added to a cooled solution of 3-iodobenzoic acid (7.41 g, 30 mmol), N-methylmorpholine (7.61 g, 8.27 mL, 75 mmol), N-methoxy-methylamine hydrochloride (3.53 g, 36 mmol) in methylene chloride (100 mL) at 0 °C. The mixture was stirred at room temperature for 3 days. Water was added and the phase separated. The aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed successively with water (2X) and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and product was purified by flash column chromatography on silica gel eluted with 17-28% ethyl acetate in hexanes to give a colorless oil (7.67 g, 88% yield); homogeneous by TLC, mass spectrum (CI) m/e 292.1 $(M+1)^+$.

Step B: 3-Iodophenyl 4-pyridylmethyl ketone

To a solution of lithium diisopropylamide (21 mmol) prepared from disopropylamine (2.12 g, 2.75 mL) in THF (40 mL) and n-butyllithium (8.4 mL of a 2.5 M solution in hexanes)) at -45 °C was added dropwise 4-picoline (1.96 g, 2.04 mL). The yellow/orange reaction mixture was stirred 1 hr at -20 to -45 °C. A solution of N-methoxy-N-methyl-3-iodobenzamide from Step A (3.015 g, 10.4 mmol) in THF (10 mL) was added dropwise at -30 °C. The stirred reaction mixture was allowed to warm to 5 °C over 4 h. The reaction was quenched by the addition of a 1/2 saturated solution of ammonium chloride (30 mL) at 0 to 5 °C. The phases were separated and the aqueous phase extracted with ethyl acetate (3 times). The combined organic layers were successively washed with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 20-65% ethyl acetate in hexanes to yield the title compound as a yellow solid (2.15 g, 64% yield), mass spectrum (CI) m/e 324.1 $(M+1)^+$.

Step C: 1-(3-Iodophenyl)-2-(4-pyridyl)ethane-1,2-dione

A mixture of 3-iodophenyl 4-pyridylmethyl ketone from Step B (3.09 g, 9.57 mmol) and selenium dioxide powder (1.062 g, 9.57 mmol) in degassed glacial acetic acid (22 mL) was heated to 90 °C for 30 min in the dark. The reaction mixture was cooled to 0 °C and ethyl acetate (30 mL) was added. A solution of potassium carbonate (26 g) in water (140 mL) was carefully added dropwise to the reaction mixture until the pH reached ~8. The organic phase was separated and the aqueous phase was treated with additional potassium carbonate solution until pH 10. The aqeuous phase was then extracted with ethyl acetate (3 times). The combined organic phases were washed successively with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 20-50% ethyl acetate in hexanes in the dark to give the title compound as a yellow solid (1.3 g, 40% yield), mass spectrum (CI) m/e 338.1 $(M+1)^+$.

Step D: 2-(4-Azidophenyl)-4-(3-iodophenyl)-5-(4-pyridyl)imidazole

[Note: It is important to perform this reaction and all subsequent manipulations including drying, rotoevaporation and column chromatography as much in the dark as possible. The product is very light sensitive.]

To a solution of 1-(3-iodophenyl)-2-(4-pyridyl)ethane-1,2-dione from Step C (1.3 g, 3.86 mmol) in glacial acetic acid (10 mL) under dry nitrogen atmosphere was added ammonium acetate (3.0 g, 39 mmol) followed by 4-azidobenzaldehyde (681 mg, 4.63 mmol). The reaction mixture was heated for 2 h. After cooling to 0 °C, ammonium hydroxide solution was added until pH 8 was obtained. The phases were separated. The aqueous phase (adjusted to pH 10 with more ammonium hydroxide solution) was extracted with ethyl acetate (3 times). The combined organic layers were washed successively with water and saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 25-80% ethyl acetate in hexanes to yield the title compound as a pale brown glass (579 mg, 33% yield), mass spectrum (CI) m/e 465.1 $(M+1)^+$.

BIOLOGICAL ASSAYS

The ability of compounds of the present invention to inhibit the binding of glucagon and the synthesis or the activity of cytokines can be determined by the following *in vitro* assays.

^{125}I-Glucagon Binding Screen with CHO/hGLUR Cells

The reagents are prepared as follows:

1M o-Phenanthroline (Aldrich #32,005-6, MW 198.23) (prepare fresh): 198.2 mg/ml ethanol

0.5M DTT (Sigma #D-9779, MW 154.2) (prepare fresh).

Protease Inhibitor Mix(1000X): 5 mg leupeptin + 10 mg benzamidine + 40 mg bacitracin + 5 mg soybean trypsin inhibitor per ml DMSO. Store aliquots at -20 °C.

250 µM Human Glucagon (Peninsula #7165,MW 3480.62): Solubilize 0.5 mg vial in 575 µl 0.1N acetic acid.Store in aliquots at -20 °C. Thus, 1 µl yields 1 µM final concentration in assay for non-specific binding.

Assay Buffer: 20 mM Tris, pH 7.8; 1 mM DTT; 3 mM o-phenanthroline.
Assay Buffer w/ 0.1% BSA (for dilution of label only, therefore 0.01% final in assay): 10 µl 10% BSA (heat-inactivated) + 990 µl assay buffer

^{125}I-Glucagon (NEN #NEX-207, receptor-grade, 2200 Ci/mmol): Dilute to 50,000 cpm/25 µl in assay buffer w/ BSA.Thus, ~50 pM final concentration in assay.

Harvesting of CHO/hGLUR Cells for Assay:

1. Remove media from confluent flask then rinse once each with PBS (Ca,Mg-free) and Enzyme-free Dissociation Fluid (Specialty Media, Inc.).

2. Add 10 ml Enzyme-free Dissoc. Fluid and hold for ~4 min. at 37 °C.

3. Gently tap cells free, triturate, take aliquot for counting and centrifuge remainder for 5 min. at 1000 rpm.

4. Resuspend pellet in assay buffer (no BSA) at 75000 cells per 100 µl.

Alternatively, membrane preparations from CHO/hGLUR cells can be used in place of whole cells at the same assay volume. Final protein concentration of membrane preparation is determined on a per batch basis.

The determination of inhibition of glucagon binding is carried out by measuring the reduction of I^{125}-glucagon binding in the presence of compounds of Formula I. The assay is carried out in a 96-well box. The following reagents are combined:

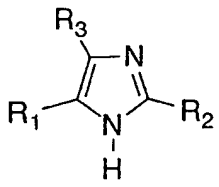
	Assay Buffer	Compound /Vehicle	250uM Glucagon	^{125}I-Glucagon	CHO/hGLUR Cells
Total Binding	120 µL	--/5 µL	--	25 µL	100 µL
+compound	120 µL	5 µL/--	--	25 µL	100 µL
NSB	120 µL	--/5 µL	1 µL	25 µL	100 µL

NSB:non specific binding

The box is incubated for 60 min. at 22 °Con a shaker at 275 rpm. The wells are filtered over pre-soaked (0.5% polyethylimine(PEI)) GF/C filtermat using an Innotech Harvester or Tomtec Harvester with four washes of ice-cold 20 mM Tris, pH 7.8 buffer. Count filters in Gamma-scintillation counter.

WHAT IS CLAIMED IS:

1. A method of treating glucagon mediated disease in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a glucagon antagonist of formula (I):



(I)

wherein

R_1 is 4-pyridyl, 4-pyrimidinyl or 4-quinolyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) halogen,

(2) -CN,

(3) C_{1-10} alkyl-, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(4) -O-C_{1-10}alkyl,

(5) -S-C_{1-10}alkyl,

(6) -NR_8R_9, and

(7) -NO_2;

R_2 is phenyl, 1-naphthyl, 2-naphthyl or heteroaryl which is unsubstituted or substituted with one, two or three substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl,

(2) R_4, and

(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4;

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to five substituents each of which is independently selected from the group consisting of

(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,
(2) -O-C_{1-2}alkyl,
(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,
(4) -O-heteroaryl,
(5) $-NO_2$,
(6) halogen,
(7) $-S-CH_3$,
(8) $-S(O)_mC_{1-2}$alkyl,
(9) $-S(O)_mOR_8$,
(10) $-S(O)_mNR_8R_9$,
(11) $-O(CR_{10}R_{20})_pNR_8R_9$,
(12) $-C(O)C_{1-2}$alkyl,
(13) $-CO_2C_{1-2}$alkyl,
(14) $-CO_2(CR_{10}R_{20})_nCONR_8R_9$,
(15) $-ZC(O)R_8$,
(16) -CN,
(17) $-C(Z)NR_8R_9$,
(18) amino,
(19) $NR_{10}C(Z)R_8$,
(20) $-C(Z)NR_8OR_9$,
(21) $NR_{10}C(Z)NR_8R_9$,
(22) $-NR_{10}S(O)_mR_{11}$,
(23) $-C(=NOR_{21})R_8$,
(24) $-NR_{10}C(=NR_{15})SR_{11}$,
(25) $-NR_{10}C(=NR_{15})NR_8R_9$,
(26) $-NR_{10}C(=CR_{14}R_{24})SR_{11}$,
(27) $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$,
(28) $-NR_{10}C(O)C(O)NR_8R_9$,
(29) $-NR_{10}C(O)C(O)OR_{10}$,
(30) $-NR_{10}S(O)mNR_7R_{17}$,

(31) -C(=NR_{13})NR_8R_9,
(32) -C(=NOR_{13})NR_8R_9,
(33) -C(=NR_{13})ZR_{11},
(34) -OC(Z)NR_8R_9,
(35) -$NR_{10}S(O)_mCF_3$,
(36) -$NR_{10}C(Z)OR_{10}$,
(37) 5-(R_{18})-1,2,4-oxadiazol-3-yl or
(38) 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

R_4 is

(1) -OR_8,
(2) -NO_2,
(3) halogen
(4) -$S(O)_mR_{11}$,
(5) -SR_8,
(6) -$S(O)_mOR_8$,
(7) -$S(O)_mNR_8R_9$,
(8) -NR_8R_9,
(9) -$O(CR_{10}R_{20})_pNR_8R_9$,
(10) -$C(O)R_8$,
(11) -CO_2R_8,
(12) -$CO_2(CR_{10}R_{20})_nCONR_8R_9$,
(13) -$ZC(O)R_8$,
(14) -CN,
(15) -$C(Z)NR_8R_9$,
(16) $NR_{10}C(Z)R_8$,
(17) -$C(Z)NR_8OR_9$,
(18) $NR_{10}C(Z)NR_8R_9$,
(19) -$NR_{10}S(O)_mR_{11}$,
(20) -C(=NOR_{21})R_8,
(21) -$NR_{10}C(=NR_{15})SR_{11}$,
(22) -$NR_{10}C(=NR_{15})NR_8R_9$,
(23) -$NR_{10}C(=CR_{14}R_{24})SR_{11}$,
(24) -$NR_{10}C(=CR_{14}R_{24})NR_8R_9$,
(25) -$NR_{10}C(O)C(O)NR_8R_9$,

(26) $-NR_{10}C(O)C(O)OR_{10}$,
(27) $-C(=NR_{13})NR_8R_9$,
(28) $-C(=NOR_{13})NR_8R_9$,
(29) $-C(=NR_{13})ZR_{11}$,
(30) $-OC(Z)NR_8R_9$,
(31) $-NR_{10}S(O)_mCF_3$,
(32) $-NR_{10}C(Z)OR_{10}$,
(33) 5-(R_{18})-1,2,4-oxadiazol-3-yl,
(34) 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl or
(35) azido;

R_7 and R_{17} are each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 and R_9 are independently selected from

(1) hydrogen,
(2) heterocyclyl,
(3) heterocyclylalkyl, and
(4) R_{11}; or

R_8 and R_9 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is
(1) C_{1-10} alkyl,
(2) halo-substituted C_{1-10} alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10} alkynyl,
(5) C_{3-7} cycloalkyl,
(6) C_{5-7} cycloalkenyl,
(7) aryl,
(8) aryl-C_{1-10} alkyl,
(9) heteroaryl or

(10) heteroaryl-C_{1-10} alkyl;

R_{12} is (1) hydrogen,

(2) -C(Z)R_{13},

(3) optionally substituted C_{1-4} alkyl,

(4) optionally substituted aryl C_{1-4} alkyl, or

(5) S(O)$_2R_{25}$;

R_{13} is (1) hydrogen, or

(2) R_{25};

R_{14} and R_{24} is each independently selected from

(1) hydrogen,

(2) alkyl,

(3) nitro or

(4) cyano;

R_{15} is (1) hydrogen,

(2) cyano,

(3) C_{1-4} alkyl,

(4) C_{3-7} cycloalkyl or

(5) aryl;

R_{18} and R_{19} is each independently selected from

(1) hydrogen,

(2) C_{1-4} alkyl,

(3) substituted alkyl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy,

(4) optionally substituted aryl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy,

(5) optionally substituted arylalkyl, wherein the substituents may be halo, C_{1-3} alkoxy, amino, or carboxy, or

R_{18} and R_{19} together denote an oxo or thioxo;

R_{21} is (1) R_{13},

(2) a pharmaceutically acceptable cation, or

(3) aroyl, or

(4) C_{1-10} alkanoyl;

R_{22} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{25} is (1) C_{1-10} alkyl,

(2) C_{3-7} cycloalkyl,
(3) heterocyclyl,
(4) aryl,
(5) aryl C_{1-10} alkyl,
(6) heterocyclyl-C_{1-10} alkyl,
(7) heteroaryl or
(8) heteroaryl C_{1-10} alkyl;

Z is oxygen or sulfur;
m is 1 or 2;
n is 1 to 10;
p is 1 to 10; or
a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein said glucagon antagonist is a compound of formula I wherein
R_1 is 4-pyridyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of
(1) halogen,
(2) -CN,
(3) C_{1-10} alkyl-, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,
(4) -O-C_{1-10}alkyl,
(5) -S-C_{1-10}alkyl,
(6) -NR_8R_9, and
(7) -NO_2.

3. The method of Claim 1 wherein said glucagon antagonist is a compound of formula I wherein
R_2 is phenyl, 1-naphthyl, 2-naphthyl or thienyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of
(1) C_{1-10} alkyl,
(2) R_4, and

(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4.

4. The method of Claim 1 wherein said glucagon antagonist is a compound of formula I wherein

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to five substituents each of which is independently selected from the group consisting of

(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(2) -O-C_{1-2}alkyl,

(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,

(4) -O-heteroaryl,

(5) -NO_2,

(6) halogen,

(7) -S-CH_3,

(8) -$S(O)_m C_{1-2}$alkyl,

(9) -$S(O)_m OR_8$.

5. The method of Claim 1 wherein said glucagon antagonist is a compound of formula I wherein

R_1 is 4-pyridyl unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(2) -O-C_{1-10}alkyl,

(3) -S-C_{1-10}alkyl,

(4) -NR_8R_9, and

(5) -NO_2;

R_2 is phenyl, 1-naphthyl, 2-naphthyl or thienyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

(1) C_{1-10} alkyl,

(2) R_4, and

(3) C_{1-10} alkyl substituted with up to 5 groups independently selected from R_4;

R_3 is phenyl, 1-naphthyl, or 2-naphthyl which is unsubstituted or substituted with up to five substituents each of which is independently selected from the group consisting of

(1) C_{1-3}alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

(2) -O-C_{1-2}alkyl,

(3) -O-aryl, where the aryl group is selected from the group consisting of phenyl and naphthyl and with the proviso that said -O-aryl group is not located at the *meta* (or 3-) position when R_3 is phenyl,

(4) -O-heteroaryl,

(5) $-NO_2$,

(6) halogen,

(7) $-S-CH_3$,

(8) $-S(O)_mC_{1-2}$alkyl,

(9) $-S(O)_mOR_8$,

R_4 is

(1) $-OR_8$,

(2) $-NO_2$,

(3) halogen

(4) $-S(O)_mR_{11}$,

(5) $-SR_8$,

(6) $-S(O)_mOR_8$,

(7) $-S(O)_mNR_8R_9$,

(8) $-NR_8R_9$,

(9) $-O(CR_{10}R_{20})_pNR_8R_9$,

(10) $-C(O)R_8$,

(11) $-CO_2R_8$,
(12) $-CO_2(CR_{10}R_{20})_nCONR_8R_9$,
(13) $-ZC(O)R_8$,
(14) -CN,
(15) $-C(Z)NR_8R_9$,
(16) $NR_{10}C(Z)R_8$,
(17) $-C(Z)NR_8OR_9$,
(18) $NR_{10}C(Z)NR_8R_9$,
(19) $-NR_{10}S(O)_mR_{11}$,
(20) azido.

6. The method of Claim 1 wherein said glucagon antagonist is selected from the group consisting of:

(1) 4-(4-fluorophenyl)-2-(4-methoxycarbonylphenyl)-5-(4-pyridyl)imidazole,
(2) 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(3) 2-(4-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(4) 4-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-(4-pyridyl)imidazole,
(5) 2-(4-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(6) 4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)imidazole,
(7) 4-(4-fluorophenyl)-2-(4-n-heptyphenyl)-5-(4-pyridyl)imidazole,
(8) 4-(4-fluorophenyl)-2-(4-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(9) 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole,
(10) 2-(4-aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(11) 2-(3-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(12) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(13) 2-(3,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(14) 4-(4-fluorophenyl)-2-(4-iodophenyl)-5-(4-pyridyl)imidazole,
(15) 2-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(16) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(4-trifluoromethylphenyl)imidazole,
(17) 2-(4-biphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(18) 4-(4-fluorophenyl)-2-(1-naphthyl)-5-(4-pyridyl)imidazole,
(19) 2-(4-ethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(20) 4-(4-fluorophenyl)-2-(2-naphthyl)-5-(4-pyridyl)imidazole,
(21) 2-(5-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(22) 4-(4-fluorophenyl)-2-(3-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(23) 2-(4-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(24) 4-(4-fluorophenyl)-2-(4-methylphenyl)-5-(4-pyridyl)imidazole,
(25) 2-(3-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(26) 2-(3-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(27) 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(28) 2-(3-bromo-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(29) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(30) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(3-trifluoromethylphenyl)imidazole,

(31) 2-(3,4-dimethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(32) 2-(3-chlorophenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,

(33) 4-(3-chlorophenyl)-2-(3,4-dichlorophenyl)-5-(4-pyridyl)imidazole,

(34) 2-(4-benzyloxyphenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,

(35) 2-(3,4-dichlorophenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(36) 2-(4-benzyloxyphenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(37) 2-(4-bromophenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(38) 2-(4-(2-chloro-6-fluorobenzyloxy)phenyl)-4-(4-fluorophenyl-5-(4-pyridyl)imidazole,

(39) 2-(4-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(40) 2-(3-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(41) 2-(3-chlorophenyl)-4-(4-iodophenyl)-5-(4-pyridyl)imidazole,

(42) 2-(4-chlorophenyl)-4-(4-bromophenyl)-5-(4-pyridyl)imidazole,

(43) 2-(4-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,

(44) 2-(3-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,

(45) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(3-methyl-4-pyridyl)imidazole,

(46) 2-(4-chlorophenyl)-4-(2-fluoro-4-trifluoromethylphenyl)-5-(4-pyridyl)imidazole,

(47) 2-(4-chlorophenyl)-4-(2-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(48) 4-(3-bromophenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,
(49) 4-(3-bromo-4-methoxyphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,
(50) 2-(4-chlorophenyl)-4-(2-ethoxyphenyl)-5-(4-pyridyl)imidazole, and
(51) 2-(4-Azidophenyl)-4-(3-iodophenyl)-5-(4-pyridyl)imidazole.

7. A compound selected from the group consisting of:
(1) 4-(4-fluorophenyl)-2-(4-methoxycarbonylphenyl)-5-(4-pyridyl)imidazole,
(2) 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(3) 2-(4-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(4) 4-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-(4-pyridyl)imidazole,
(5) 2-(4-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(6) 4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)imidazole,
(7) 4-(4-fluorophenyl)-2-(4-n-heptyphenyl)-5-(4-pyridyl)imidazole,
(8) 4-(4-fluorophenyl)-2-(4-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(9) 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole,
(10) 2-(4-aminophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(11) 2-(3-bromophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(12) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(13) 2-(3,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(14) 4-(4-fluorophenyl)-2-(4-iodophenyl)-5-(4-pyridyl)imidazole,
(15) 2-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(16) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(4-trifluoromethylphenyl)imidazole,
(17) 2-(4-biphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(18) 4-(4-fluorophenyl)-2-(1-naphthyl)-5-(4-pyridyl)imidazole,
(19) 2-(4-ethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(20) 4-(4-fluorophenyl)-2-(2-naphthyl)-5-(4-pyridyl)imidazole,
(21) 2-(5-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(22) 4-(4-fluorophenyl)-2-(3-phenoxyphenyl)-5-(4-pyridyl)imidazole,
(23) 2-(4-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(24) 4-(4-fluorophenyl)-2-(4-methylphenyl)-5-(4-pyridyl)imidazole,
(25) 2-(3-benzyloxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(26) 2-(3-chlorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(27) 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(28) 2-(3-bromo-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,
(29) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(30) 4-(4-fluorophenyl)-5-(4-pyridyl)-2-(3-trifluoromethylphenyl)imidazole,

(31) 2-(3,4-dimethylphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole,

(32) 2-(3-chlorophenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,

(33) 4-(3-chlorophenyl)-2-(3,4-dichlorophenyl)-5-(4-pyridyl)imidazole,

(34) 2-(4-benzyloxyphenyl)-4-(3-chlorophenyl)-5-(4-pyridyl)imidazole,

(35) 2-(3,4-dichlorophenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(36) 2-(4-benzyloxyphenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(37) 2-(4-bromophenyl)-4-phenyl-5-(4-pyridyl)imidazole,

(38) 2-(4-(2-chloro-6-fluorobenzyloxy)phenyl)-4-(4-fluorophenyl-5-(4-pyridyl)imidazole,

(39) 2-(4-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(40) 2-(3-chlorophenyl)-4-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(41) 2-(3-chlorophenyl)-4-(4-iodophenyl)-5-(4-pyridyl)imidazole,

(42) 2-(4-chlorophenyl)-4-(4-bromophenyl)-5-(4-pyridyl)imidazole,

(43) 2-(4-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,

(44) 2-(3-chlorophenyl)-5-(4-pyridyl)-4-(4-trifluoromethylphenyl)imidazole,

(45) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-(3-methyl-4-pyridyl)imidazole,

(46) 2-(4-chlorophenyl)-4-(2-fluoro-4-trifluoromethylphenyl)-5-(4-pyridyl)imidazole,

(47) 2-(4-chlorophenyl)-4-(2-phenoxyphenyl)-5-(4-pyridyl)imidazole,

(48) 4-(3-bromophenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(49) 4-(3-bromo-4-methoxyphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)imidazole,

(50) 2-(4-chlorophenyl)-4-(2-ethoxyphenyl)-5-(4-pyridyl)imidazole, and

(51) 2-(4-Azidophenyl)-4-(3-iodophenyl)-5-(4-pyridyl)imidazole.

7. A method of Claim 1 wherein said glucagon mediated disease is diabetes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/20955

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44
US CL :514/341

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,772,441 A (LOMBARDINO) 13 November 1973.	1-7
A,P	US 5,620,999 A (WEIER et al.) 15 April 1997.	1-7
A,P	US 5,686,455 A (ADAMS et al.) 11 November 1997.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search
12 JANUARY 1998

Date of mailing of the international search report
10 FEB 1998

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Form PCT/ISA/210 (second sheet)(July 1992)*